

The 35 U.S.C. §102(b) Rejection:

Claims 1-4 and 6 stand rejected under 35 U.S.C. §102(b) as being anticipated by **Cummins, Jr.** This rejection is respectfully traversed. The Examiner cites column 4, lines 19-36, col. 5, lines 50-55, col. 6, lines 12-26, col. 13 and the claims of **Cummins** to support this rejection. Column 4, lines 19-36 discuss the types of disease conditions in which the **Cummins** patent might be employed, namely: "...apparent autoimmune disorders characterized by a chronic tissue degenerative inflammatory condition. Diseases so characterized include multiple sclerosis, rheumatoid arthritis, stomatitis, and lupus erythematosus." Conditions supported by actual clinical data in the prior art are predominantly veterinary applications, such as "canine lupus erythematosus". Of the human cases pertaining to autoimmune conditions, there is only one anecdotal report of a multiple sclerosis patient treated. The other cases are either not autoimmune conditions (cancers, acne, viral warts) or maladies for which an autoimmune etiology remain controversial (rheumatoid arthritis, stomatitis).

Applicant argues this extremely limited clinical data is far from enabling and hence cannot be considered anticipatory. **Cummins** describes in column 12 that a female with multiple sclerosis "received

treatment in accordance with the present invention" and "had no recurrence...for the past nine months". Apart from the consideration that such a disorder is characterized by remission and relapse as is known in the art, **Cummins** provides absolutely no credible evidence that Applicant's invention could be made or was in fact made. Similarly, the **Cummins** descriptions of treating malignant lymphoma, mesothelioma and aphthous stomatitis are also anecdotal. A person having ordinary skill in this art would clearly consider these anecdotal descriptions as literally incredible and therefore non-enabling.

As the Supreme Court held in *Seymour v. Osbourne*, 78 U.S. (11 Wall.) 516 (1870) a non-enabling reference is not anticipatory prior art under 35 USC § 102. See, also, *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241 (Fed. Cir. 1986); *In re Wiggins*, 179 USPQ 421 (CCPA 1973); *In re Brown* 141 USPQ 245 (CCPA 1964). That is, to be an anticipatory reference under 35 USC §102, the prior art must be enabling to the same degree as an invention seeking patent protection under 35 U.S.C §112, first paragraph.

Applicant's invention targets a much broader spectrum of autoimmune conditions than **Cummins** and, more importantly, presents substantive clinical data in support. In marked contrast to the

one multiple sclerosis patient presented in the prior art, the instant invention contains data from 27 multiple sclerosis patients and 18 control patients. . Animal data presented is from, e.g., two well established models of human autoimmune disease, experimental allergic encephalitis/neuritis and the NOD mouse, a model for human autoimmune diabetes mellitus.

Further, the **Cummins** claims are limited to treating viral diseases. Applicant respectfully submits that the instant invention as presently claimed falls outside the scope of the **Cummins** disclosure. **Cummins** repeatedly emphasizes the criticality of maintaining the interferon in contact with the oral and pharyngeal mucosa for the purposes of treating viral diseases. Applicant's claims specifically point out that Applicant's method requires ingestion of the interferon. Indeed, Applicant's specification shows the necessity of the interferon interacting with intestinal sites and Peyer's patches.

The section of **Cummins** cited by the Examiner (col. 4, lines 19-36) in support of the rejection under 35 U.S.C. §102(b) also presents the suggested dosage for the therapeutic agent. This is much different than the one presented in the instant invention—"...more preferably 0.5

to about 1.5 IU/lb of body weight per day” as compared to 50 –25,000 IU/kg every other day.

Finally, with respect to the route of administration presented in col. 4, lines 19-36 of **Cummins**, Applicant's claim 1 recites “A method of treating an auto-immune disease in an animal comprising the step of orally administering a type one interferon to said animal **such that the type one interferon is ingested after oral administration.**” (emphasis added). This is clearly distinct from **Cummins**, which emphasizes a different mode of absorption: “...in a dosage form adapted to promote contact of said dosage of interferon with the oral and pharyngeal mucosa of said animal.” (emphasis added).

As one of the accompanying 37 CFR Rule 1.132 Declarations points out, **Cummins** “stresses that administration of interferon should be directed at absorption through the oral mucosa, and not the gastric mucosa. Maximal contact with the oral or pharyngeal mucosa is emphasized, contact with the gastric or intestinal mucosa is considered therapeutically nugatory.” This is contrasted with Applicant's invention, in the other accompanying 37 CFR Rule 1.132 Declaration:

In Applicant's animal experiments, **the interferon was fed through a needle inserted directly into the stomach or duodenum of the animal, i.e., there was no contact with the oral or pharyngeal mucosa.** In Applicant's clinical studies with human subjects, the interferon was "ingested", which briefly exposed the oral mucosa to the interferon, but **no attempts at maximizing contact with the oral mucosa were made nor would there have been any significant absorption of the alpha-interferon through the oral or pharyngeal mucosa.** (emphasis added).

Examiner cites col. 5, lines 50-55 of **Cummins** in support of the rejection of Claims 1-4 and 6 under 35 U.S.C. §102(b). This section teaches the dosage of the therapeutic agent, viz.:

"Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days treatment per week or month, can be used as an alternative to continuous daily treatment." (emphasis added).

Applicant contends that this does not anticipate the instant invention, as it teaches a multiple-dose daily regimen. Additionally, the descriptive clinical lore of the **Cummins** patent can in no way be said to anticipate Applicant's substantive data.

Examiner further cites col. 6, lines 12-26 to support the rejection of Claims 1-4 and 6 under 35 U.S.C. §102(b). Applicant argues that this is an explicit teaching away from the present invention. Lines 12-16 of col. 6 of **Cummins** make this point clearly:

It is also contemplated by the present invention to provide interferon in a solid dosage form such as a lozenges (sic) adapted to be dissolved upon contact with saliva in the mouth with or without the assistance of chewing.

As stated in the Specification, the interferon dosage of the instant invention can be said to by-pass the mouth, see, e.g. Example 11.

As stated *supra*, interferon is orally administered by placing a 2.5 cm syringe fitted with a 20 gauge ball point needle in the posterior oropharyngeal region of the oral cavity and delivering the type one interferon dose directly to the distal esophagus, stomach, and proximal

small intestine (as verified experimentally by injecting Evans blue during routine feeding and subsequent sacrifice).

Thus, Applicant maintains that there are such substantive differences between the method of **Cummins** and the claimed invention. Declarations under 37 CFR 1.132 are provided herewith, which support and extend Applicant's arguments. Accordingly, Applicant requests that the rejection of Claims 1-4 and 6 under 35 U.S.C. §102 as being anticipated by **Cummins** be withdrawn.

The 35 U.S.C. §103 Rejections:

Claim 5 stands rejected under 35 U.S.C. §103 as being unpatentable over **Cummins, Jr.** (US Patent 5,019,382). This rejection is traversed.

As stated above, the **Cummins** patent teaches the dosage of the therapeutic agent:

“Daily dosage of interferon can be administered as a single dosage, or, preferably, it is divided and administered in a multiple-dose daily regimen. A staggered regimen, for example one to three days

treatment per week or month, can be used as an alternative to continuous daily treatment.” (emphasis added).

Applicant contends that the dosage regimen delineated in Claim 5 is not rendered obvious by **Cummins**. The instant invention teaches an every other day dosing. This is alluded to as a less preferred method of administering interferon by **Cummins**, which teaches a multiple-dose daily regimen.

Examiner further states that claims 1-18 stand rejected under 35 U.S.C. §103 as being unpatentable over **Cummins** in view of **Shibutani et al.** and further in view of **Sobel** (abstract of WO 94/20122 or U.S. Patent 5,624,895). This rejection is traversed.

Applicant respectfully asserts that the cited references do not render the present invention obvious under 35 U.S.C. Section §103 for the reasons cited above in response to the 35 U.S.C. Section §102 rejection. The **Shibutani** abstract is simply a description of a lack of toxicity of human beta interferon in mice and rats. It does not disclose, teach or suggest in any form a method of treating auto-immune disease in an animal comprising the step of orally administering a type one

interferon to said animal such that the type one interferon is ingested after oral administration as disclosed in the instant application.

This issue of dosage is addressed in both Rule 1.132 Declarations. First, one very valuable feature of the instant invention is its precise delineation of a dose-response relationship for the oral administration of type I interferons to treat autoimmune diseases. Secondly, there is no overlap between the doses suggested by **Cummins** and doses found to be effective in the present invention. The latter are significantly higher (by about two orders of magnitude) than the maximum dose of **Cummins**.

**Sobel**, WO 94/20122 is an abstract for a patent application which describes methods of treating "an asymptomatic preclinical autoimmune state in a mammal" or inhibiting "rejection of transplanted islet cells or a pancreas in a mammal". These methods do not pertain to the instant invention.

Further, **Sobel** (U.S. Patent 5,624,895) expressly teaches away from the instant invention. Pages 53 and 54 of Applicant's specification describe that reduction of interferon gamma levels following administration of type I interferons (alpha and/or beta) may in some way ameliorate the severity of the autoimmune disease:

"At day 13 after immunization, in situ IFN- $\gamma$  production was reduced together with inflammation...**In combination, the present invention demonstrates that oral administration of IFN  $\alpha/\beta$  reduces the severity of experimental allergic neuritis by a reduction in IFN- $\gamma$  production...** Parenteral IFN- $\gamma$  administration has been shown to augment both myelin-induced and T-cell mediated experimental allergic neuritis... while the opposite effect was obtained by parenteral administration of anti-IFN- $\gamma$  antibody...Decreased IFN- $\gamma$  and inflammation in early stages and diminished demyelination at later stages of disease suggest a critical role for IFN- $\gamma$  in the pathogenesis of experimental allergic neuritis." (emphasis added).

In contrast, the **Sobel** patent teaches the 'surprising' therapeutic application of IFN-~~for~~ autoimmune diabetes. As is explained in both Rule 1.132 Declarations, simply because gamma interferon is also an interferon does not mean its potential use renders the application of a different class of interferons obvious.

While **Cummins** describes unsubstantiated anecdotal stories, **Cummins** does not enable Applicant's invention and place Applicant's invention in the hands of a person having ordinary skill in this art. Nor do the other references alone, or in combination with **Cummins**. Both Rule 1.132 Declarations point out a person with ordinary skill in the art would not have expected any clinical effects from orally administered alpha interferon. Proteins such as interferons are broken down in the gastrointestinal tract when ingested and would be expected to be biologically inactive

Hence, no such teaching, suggestion or incentive may be gleaned from any of the references relied upon by the Examiner. Thus, Applicant respectfully submits that the cited references do not render the claimed invention obvious. Accordingly, Applicant respectfully requests that the rejection of Claims 1-18 under 35 U.S.C. §103 be withdrawn.

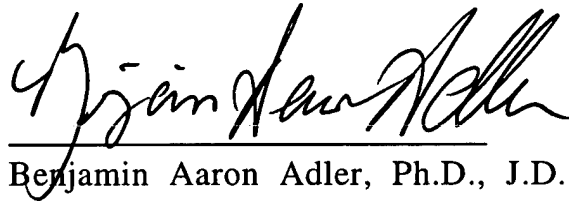
The Specification has been modified to identify the previous continuation-in-part serial number. Additionally, a new Declaration is included with this response, per Examiner's request.

This is intended to be a complete response to the Office Action mailed March 27, 1998. If any issues remain outstanding, the

Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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Benjamin Aaron Adler, Ph.D., J.D.  
Registration No. 35,423  
Counsel for Applicant

McGREGOR & ADLER, LLP  
8011 Candle Lane  
Houston, Texas 77071  
(713) 777-2321  
BAADLER@flash.net